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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/237,291	01/25/99	YOUNG	J SYS-2068

001095
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EXAMINER	
SCHMIDT,M	
ART UNIT	**PAPER NUMBER**
1635	3

DATE MAILED: 05/12/99

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
09/237,291	Young et al.
Examiner	**Group Art Unit**
Schmidt	1635

—The MAILING DATE of this communication appears on the cover sheet beneath the correspondence address—

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, such period shall, by default, expire SIX (6) MONTHS from the mailing date of this communication .
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).

Status

☐ Responsive to communication(s) filed on _____.

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle,* 1935 C.D. 1 1; 453 O.G. 213.

Disposition of Claims

☒ Claim(s) 1-30 is/are pending in the application.

Of the above claim(s) 1-17 is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) 18-30 is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claim(s) _____ are subject to restriction or election requirement.

Application Papers

☒ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119 (a)-(d)

☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 11 9(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 1 7.2(a)).

*Certified copies not received: _____.

Attachment(s)

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☒ Notice of Reference(s) Cited, PTO-892

☒ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Interview Summary, PTO-413

☐ Notice of Informal Patent Application, PTO-152

☐ Other _____

Office Action Summary

DETAILED ACTION

1. Restriction to one of the following inventions is required under 35 U.S.C. 121:

   I. Claims 1-9, drawn to a method for promoting the expansion of hematopoietic stem cells in culture, classifiable in class 435, subclass 383.

   II. Claims 10-17, drawn to a method of restoring hematopoietic capability in a subject, classifiable in class 424, subclass 93.7.

   III. Claims 18-30, drawn to a method of modifying a hematopoietic stem cell, classifiable in class 435, subclass 455.

2. The inventions are distinct, each from the other because of the following reasons:

Group I, group II and group III are drawn to distinct methods involving cultured hematopoietic stem cells. Group I is a method for expansion of the hematopoietic stem cells in culture. Group II is drawn to a method of restoring hematopoietic capability in a subject by application of an expanded population of stem cells. Group III is drawn to a method of recombinantly modifying a hematopoietic stem cell by delivery of a nucleic acid. These groups are patentably distinct based on their different scientific considerations and as such are unrelated inventions because Group I considers cells in culture and their survival in a media solution, Group II considers therapeutic treatment of a whole organism which considers delivery of cells, toxicity, etc., and Group III considers further administration of a nucleic acid to cells for recombinant therapy of the cells in culture which involves specificity, availability of the target, and visualization of desired results.

Because these inventions are distinct for the reasons given above and have acquired a separate status in the art as shown by their different classification, because of their recognized divergent subject matter, and the search required for Groups I, II or III is not required for the other Groups, because the Groups do not substantially overlap and thus restriction for examination purposes as indicated is proper.

During a telephone conversation with Lynn Marcus-Wyner on March 22, 1999, a provisional election was made with traverse to prosecute the invention of Group III, claims 18-30. Affirmation of this election must be made by applicant in replying to this Office action. Claims 1-17 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a petition under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(I).

Claim Rejections - 35 USC § 112

3. Claim 21 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 21 contains a typographical error, "form" should read "from."

4. Claims 18-30 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claims 18-22 are drawn to a method for modifying a hematopoetic stem cells by transforming the cell with a polynucleotide sequence. The cells are cultured with an mpl ligand and an flt3 ligand, and optionally, a c-kit ligand, and/or IL3. The polynucleotide sequence may encode a peptide, ribozyme or indecence and may be delivered via a retroviral vector, a DNA vector and/or a liposome. Claims 23-30 are drawn to the same basic method as claims 18-22, except the cells are cultured in TPO, a flt3 ligand and IL6, and optionally with LIF, IL3, a c-kit ligand, and/or fibronectin or RetroNectin.

The specification as filed teaches the role of various cytokines on the maintenance of CD34+Thy-1+cells in culture. After isolation of $CD34^+$ $Thy\text{-}1^+Lin^-$ cells from adult human bone marrow, the cells were cultured in IL-3, IL-6, LIF, TPO, FL and KL. The specification teaches

that after 6 days, 75% of the IL-3/IL-6/LIF cells had not divided. The $CD34^{hi}$ or ^{lo}/$PKH26^{lo}$ were selected for SCID-hu bone repopulation and fetal human graft. Fig. 4 and Table 4 teach that cultured $CD34^{hi}PKH^{lo}$ cells yielded the same graft results as the uncultured cells and therefore the repopulating capacity was retained. The specification teaches that culturing cells in different cytokines as in figure 5 and cultures having TPO and FL or KL had the greatest fold increase in cell number after 90 days. Example 8 teaches transfer of the L Mily vector expressing Lyt2 or the LMTNL vector for analysis of the rev gene marking to the cultured cells and table 6 teaches the results after 5 weeks. Tables 7 and 8 teach the % of the cell population expressing lyt2 in culture and table 9 compares the results of the culture to skin grafts. Example 9 teaches an increase in transformation efficiency for expression of Lyt2 in cell culture after using RetroNectin™.

Further, on page 26, the specification teaches prophetically promoters on vectors, such as Granzyme A for expression in T-cells, CD34 for expression in stem and progenitor cells, CD8 for expression in cytotoxic T-cells, and CD11b for expression in myeloid cells.

Claim 18 is broadly drawn to modification of any hematopoietic stem cell, ie. including any species, with any polynucleotide transgene while the cells are cultured with any mlp ligand and a flp ligand. The specification as filed teaches by way of example specific cytokine formulations for cell culture which vary widely in effect on the cell population and further on the transformation and transgene expression success.

There is a high level of unpredictability in the transgenic stem cell art for expression of transgenes in cultured stem cells. The level of skill in the transgenic art is such that one cannot

predict whether a transgene that is expressed in one species of hemaotopoietic cells will also be expressed efficiently in another mammalian hematopoietic cell type. For example, Strojek and Wagner (Genetic Engineering 1988) taught that a high degree of expression of a transgene in a mouse is often not predictive of a high expression in other species, because for example, the cis acting elements may interact with different trans-acting factors in the other species.

Furthermore, the specification only teaches by way of example expression of Lyt2, and no such success is taught for expression of other peptides, ribozymes, or indecence sequences. No guidelines in the specification as filed are taught as to how to overcome the unpredictability in the transgene art for expression in different species of mammalian hematopoetic cells, nor is it clear that the expression of Lyt2 is representative of expression of any transgene in any mammalian hematopoetic cell.

The expression of ribozymes and indecence in any cell type is a highly unpredictable art. The factors considered barriers to successful delivery of indecence or ribozymes are: (1) penetration of the plasma membrane of the target cells to reach the target site in the cytoplasm or nucleus, (2) withstanding enzymatic degradation, and (3) the ability to find and bind the target site and simultaneously avoid non-specific binding (see Branch). Despite the synthesis of more resilient, nuclease resistant, oligonucleotide backbones and isolated successes with indecence therapy *in vivo*, the majority of designed indecence molecules still face the challenge of successful entry and localization to the intended target and further such that indecence or ribozyme and other effects can routinely be obtained. Note Branch who further teaches the state of the art for

designing an indecence or ribozyme which inhibits a target: it "is very difficult to predict what portions of an RNA molecule will be accessible..., effective indecence molecules must be found empirically by screening a large number of candidates for their ability to act inside cells (Branch, p.49)." And in the instant case, the claims read broadly on application of any indecence or ribozyme inhibitor in any hematopoietic cultured stem cells while the specification does not teach any specific indecence or ribozymes except prophetically.

The specification as filed only provides enabling disclosure for a method of culturing $CD34^+$ $Thy\text{-}1^+Lin^-$ cells from adult human bone marrow in specific combinations of IL-3, IL-6, LIF, TPO, FL and KL which show evidence of success, ie. as claimed to provide "an effective amount," and for expression of the Lyt2 construct exemplified. The invention as broadly claimed to any species of hematopoetic stem cell and cultured in any mpl and flt3 ligand, and further, with transgenic application of any nucleic acid construct to the cells, is not enabled for the broad scope claimed. The lack of guidance in the specification as filed for: (1) cells other than human, (2) nucleic acid constructs expressing other genes, including indecence or ribozymes, and from different promoters, as well as (3) different combinations of cytokines in the cell culture, would require "trial and error" experimentation beyond which is taught by the specification as filed. The quantity of experimentation would require expression of large genus of different transgenes in hematopoetic stem cells from a large genus of mammalian species, and further optimized application of known cytokines for enablement of the invention as broadly claimed because of the level of unpredictability in the transgene modified stem cell art and the lack of guidance in the

specification as filed. Therefore, it would require undue experimentation to practice the invention as claimed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to *Mary M. Schmidt*, whose telephone number is (703) 308-4471.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, *George Elliott, Ph.D.* may be reached at (703) 308-4003. The examiner's primary, *John LeGuyader*, may be reached at (703) 308-0447.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.